Lasers for hyperpigmentation and melasma

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Abstract
Melasma is one of the most commonly-acquired hypermelanosis of skin exposed to the sun. Treatments including hypopigmenting agents and chemical peels have been used, but at present no pharmacologic agent has been universally recognised as effective for the treatment of melasma. Recently, the Q-switched Nd:YAG laser has been proposed. This evaluation confirms how, by minimising side-effects, treatment time and costs, the Q-switched Nd:YAG laser can be effective and safe for lightening cutaneous hyperpigmentation. The biological role of cutaneous blood vessels in the pathogenesis of melasma is an interesting topic and opens new therapeutic perspectives. The authors recently performed a prospective study for evaluating the effects of pulsed dye laser (PDL) therapy. After a multispectral study for evaluating haemoglobin and melanin components, the authors are now using this vascular laser with low-fluence and have obtained some improvements. It would be tempting to think that the action of PDL on the vascularisation might have played an important role in preventing relapse. By targeting vascularity, and at least some part of the elastosis in the melasma lesions, it might be possible to decrease the stimulation of melanocytes and thus reduce the incidence of relapse.

Keywords
melasma, hyperpigmentation, laser, pulsed light

Hyperpigmentary disorders, particularly melasma and other forms of primary and secondary hyperpigmentation, can cause significant social and emotional stress in patients. Management is often challenging owing to the limited number of successful treatment options currently available. Different therapeutic methods have been used that can be divided into topical and cosmetic treatments (with depigmenting agents such as hydroquinone, methimazole, picobenzone, tretinoin, arbutin, azelaic acid, ellagic acid, mequinol, ascorbic acid, and resveratrol) alone or in combination with chemical peels or physical treatments.

Laser devices have revolutionised the treatment of many dermatological conditions, including pigmented disorders. They have been widely used with variable levels of success for the treatment of pigmented conditions such as Becker’s nevus, café au lait macules, nevus of Ota, nevocellular nevus, lentigines, tattoos, melasma, and post-inflammatory hyperpigmentation (PIH). Although many pigmented disorders have shown good results with laser treatment, the efficacy and safety of lasers for melasma is still controversial, with most authors citing chemical peels as the most effective treatment option.

Laser treatment of pigmented lesions is based on the theory of selective photothermolysis, which entails a specific wavelength of energy delivered in a shorter period of time than the thermal relaxation time ($\tau_r$) of the target chromophore, meaning that the energy is restricted to the target, thus causing less damage to the surrounding tissue. A selective window for targeting melanin lies between 630 nm and 1100 nm, where there is good skin penetration and preferential absorption of melanin over oxyhaemoglobin. Absorption of the melanin decreases as the wavelength increases, but a longer wavelength allows for deeper skin penetration. Shorter wavelengths (<600 nm) damage pigmented cells with lower energy fluencies, while longer wavelengths (>600 nm) penetrate deeper, but need more energy to cause melanocytic...
Figure 1: Pigmented blotches on the right side of the face

Figure 2: Typical erythema immediately after a session of Q-switched Nd:YAG laser (Duolite QS, DEKA Laser, Florence, Italy)

Figure 3: The disappearance of the pigmented lesions

Q-switched lasers

The τr of melanosomes ranges between 50 ns and 500 ns with a broad melanin absorption spectrum. Q-switched lasers (Nd:YAG, ruby, and alexandrite) deliver pulses lasting nanoseconds; therefore, they selectively target melanosomes with minimal thermal diffusion.

Q-switched ruby

The QS ruby laser, with a wavelength of 694 nm, is more selective for melanin than the QS Nd:YAG laser (1064 nm). Theoretically, therefore, it is expected to be more effective than QS Nd:YAG, but the role of the ruby laser is controversial, with studies showing conflicting results. In particular, one disadvantage is that a deeply pigmented epidermis can impede light penetration to the dermis and unwanted epidermal injury may result in dyspigmentation. In general, the QS ruby laser is not recommended for the treatment of hyperpigmentation disorders in darker-skinned patients (Fitzpatrick types IV-VI).

Q-switched Nd:YAG

The 532 nm QS Nd:YAG is well absorbed by melanin and being a longer wavelength, causes minimal damage to the epidermis and is not absorbed by haemoglobin. The deeper skin penetration also allows the physician to target the dermal melanin. The low-dose QS Nd:YAG laser induces sub-lethal injury to melanosomes, causing fragmentation and rupturing of the melanin granules into cytoplasm. This effect is highly selective for melanosomes as the wavelength is well absorbed by the micro-areas of ablative and thermal damage (microthermal zones; mTZ) alternated with healthy tissue. In the treated micro-areas, controlled heat release produces immediate tissue shrinkage and stimulates neocollagenesis. The areas of healthy tissue between the treated areas ensure rapid tissue repair and a drastic reduction in recovery time and post-treatment erythema. This exclusive emission system makes it possible to control tissue damage while simultaneously maximising efficacy, with repair of the damaged areas within 1 day and the disappearance of postoperative erythema usually within 3–4 days.
melanin in other structures (Figures 1-3). The QS Nd:YAG, with its longer wavelength, is the safest type of laser for treating darker skinned patients.\textsuperscript{11-12}

**Q-switched alexandrite**
The longer 755 nm wavelength of the QS alexandrite laser allows for deeper penetration into the skin. Unlike others in Q-switched range, the alexandrite laser can be used in short pulse (5 ms) emissions (Figure 5). This type of laser enables selective damage of the pigmentation; however, there is a higher risk of dyschromia, rather than scarring or post-treatment hyperpigmentation. A number of studies suggest that a possible combination of low-energy QS alexandrite and QS Nd:YAG may also be effective in treating hyperpigmentation, especially that of the 'light brown' variety.\textsuperscript{13-14}

**Intense pulsed light**
IPL is a non-laser light source that emits light in the range of 515 nm (red/yellow) to 1200 nm (infrared). The advantage of IPL is the versatility of the parameters. The wavelength, fluence, number, duration, and delay of pulses can be adapted to each patient in order to effectively target the chromophores. It can therefore be used to treat a variety of conditions, including vascular lesions, melanocytic lesions, and for hair reduction.\textsuperscript{15}

In the authors' experience, the use of IPL enables ablation of very superficial pigmented lesions with partially selective thermal damage and a low incidence of scarring, but with a high risk of discoloration (Figures 4-5). The laser settings play an important role in the treatment. Initially, 500-550 nm filters can be used for epidermal lesions, while higher wavelength filters can be used to target deeper melanin, for example, in patients with dermal/mixed melasma. The fluence can be adapted to suit the treatment sites: a higher fluence can be used for cheeks and zygoma, while the areas surrounding the eyes and neck require lower fluences. Higher fluences are useful for deeper lesions, but can cause PIH in darker-skinned patients. Single pulses are effective in heating the pigment, but double or triple pulses should be used as they reduce thermal damage, allowing the epidermis to cool while the target stays warm.\textsuperscript{16-18}

**Melasma**
Melasma is a commonly-acquired, localized hyperpigmentation disorder characterized by irregular brown or gray-brown macules and patches with well-defined margins that occur symmetrically on sun-exposed areas of the body, usually the face.\textsuperscript{19-20} This condition typically affects women of child-bearing age, and solar and UV exposure are the best known aetiologic factors. Histological and immunohistochemical studies have shown that melasma skin presents features of prominent solar damaged skin. UV irradiation is known to increase the synthesis of alpha-melanocyte-stimulating hormone (\(\alpha\)-MSH) and adrenocorticotrophic hormone (ACTH) derived from proopiomelanocortin (POMC) in keratinocytes. These peptides lead to the proliferation of melanocytes, as well as an increase in melanin synthesis via stimulation of tyrosinase activity and tyrosinase-related protein-1 (TRP-1).\textsuperscript{21}

One study has shown that melasma is characterized by alterations in the dermal structures in addition to pigmentary changes; suggesting a role of the dermis in melasma development.\textsuperscript{22} The role of fibroblasts in melasma development has also been suggested. In fact, the over-expression of both stem cell factors (SCFs) from fibroblasts and c-kits has been found: the fibroblast-derived cytokines stimulate proliferation and melanogenesis of melanocytes in culture. Therefore, it is possible that the dermal inflammation induced by an accumulation of UV irradiation may be associated with the activation of fibroblasts, which results in the upregulation of SCFs in dermal melasma, leading to increased melanogenesis.\textsuperscript{22} Recent data has also shown that melasma lesions have greater vascularization than normal perilesional skin. An increased expression of the vascular endothelial growth factor (VEGF) in keratinocytes has been suggested as a major angiogenic factor for altered vessels in melasma, therefore, the network of cellular interactions between keratinocytes, fibroblasts and perhaps vasculatures and melanocytes...
During chronic sun exposure may play an important role in the development of melasma, working in conjunction to stimulate melanocytes, resulting in epidermal hyperpigmentation.

Melasma can be classified depending on the site of the lesions (craniofacial, malar, mandibular), histological depth of the pigmentation (epidermal, dermal, mixed), and appearance under the Wood’s lamp (epidermal, dermal, mixed, indeterminate):

- **Epidermal**: light brown with an enhancement of pigmentation under the Wood’s lamp. Histologically characterised by a melanin increase in the basal, suprabasal and stratum corneum layers
- **Dermal**: ashen or blue–grey with no enhancement of pigmentation under the Wood’s lamp. Histologically there is a predominance of melanophages in the superficial and deep dermis
- **Mixed**: dark brown with enhancement of pigmentation under the Wood’s lamp in some areas only
- **Indeterminate**: not detected under the Wood’s lamp.

The best therapeutic results are normally achieved in epidermal melasma. The laser to be used must be selectively chosen and should generally be used in cases in which there is proven resistance to conventional treatments.

**Q-switched lasers**

In the past, attempts to treat melasma with lasers that targeted melanin, such as the QS ruby laser (694nm), short-pulsed green dye laser (504-510nm), QS neodymium laser (1064nm), and argon laser (514nm), yielded disappointing results. For example, in a randomised controlled trial conducted by Wattanakrai et al. 22 patients with dermal or mixed melasma were treated with the same laser at a fluence of 3-3.8 J/cm² for five sessions at 1-week intervals. The treatment was combined with 2% hydroquinone and compared with hydroquinone alone. There was a 92.5% improvement, which was significant compared with the control group. However, 136% of patients developed faint, spotty hypopigmentation that improved during follow-up. Furthermore, 18% of patients developed rebound hyperpigmentation, and all patients had a recurrence of melasma.

Jeong et al. compared the clinical efficacy and adverse effects of the low fluence QS NdYAG (1064nm) laser when performed before and after treatment with topical triple-combination (TC) creams using a split-face cross-over design in 13 patients with melasma. They used a collimated 5-7ns pulse width, 7mm spot size, and a fluence of 16-20 J/cm². Weekly sessions were carried out for 8 weeks. The laser was compared with pre- or post-treatment TC cream. The authors found that pre-treatment with TC creams was more effective as this decreases melanin production before laser injury; therefore the risk of PIH is reduced and the melasma improves. If TC cream is used after laser treatment, the melanin is produced at full capacity with a higher risk of PIH and less improvement in the melasma. Consequently, the authors recommend medical treatment for hyperpigmentation for at least 8 weeks before laser treatment in order to achieve optimal results.

Kauvar assessed the safety and efficacy of a procedure combining microdermabrasion, a topical regimen, and low fluence QS NdYAG laser treatment in 27 female subjects. In particular, low fluence QS NdYAG laser treatment of 16-2 J/cm² with 5mm or 6mm spot was administered immediately after microdermabrasion. Treatments were repeated at 4-week intervals. Twenty two subjects (81%) had more than 75% clearance of melasma, 11 subjects (40%) achieved more than 95% clearance. Most subjects showed more than 50% clearance of their melasma 1 month after the first treatment. Side-effects were limited to mild post-treatment erythema, which developed after the microdermabrasion and lasted approximately 30-60 minutes. Remission lasted for at least 6 months.
**CO₂ and IPL**

Better results can be obtained with Er:YAG laser resurfacing, and the combination of pulsed CO₂ laser and QS alexandrite laser as the CO₂ laser destroys the melanocytes, while the alexandrite laser removes the pigment left in the dermis. IPL is a non-coherent, broad-spectrum light source that emits a continuous spectrum in the range of 500nm to 1200nm. Its therapeutic efficacy is relatively higher in patients with epidermal melasma than those with mixed melasma. This phenomenon could possibly be related to the location of the melanin. In epidermal melasma, the melanosomes in the epidermis rapidly migrate to the skin surface and shed off with microcrusts. In mixed melasma, the melanin-laden macrophages in the dermis are barely damaged. In a 2010 study, Zoccali et al had excellent results with the use of IPL in melasma; they treated 38 patients (with Fitzpatrick phototypes III-IV) with IPL over three-to-five sessions at intervals of 40-45 days, using a 550nm handpiece since it offers great selectivity for melanin and reaches the deeper epidermises, two pulses of 5-10ms with a 10-20ms delay between pulses, while the fluence was modulated with regard to the anatomic area. Energy levels of 12-14J/cm² were used to treat the cheeks and zygoma, 10-12J/cm² for the forehead, while lower levels (7-8J/cm²) were used on the area around the eyes and neck. Results were excellent in 18 patients (47.37%), good in 11 (28.95%), moderate in five (13.16%), and poor in four cases (10.52%), in which a recurrence of hyperpigmented areas occurred within 2-4 months. Side effects were minimal and included a burning sensation during treatment and erythema for a short period. Possible complications included transitory hyperpigmentation, persistent hypopigmentation, and rarely, scarring.

A 10-week, split-face study by Goldman et al evaluated the safety and efficacy of TC cream when used sequentially with IPL in patients with moderate to severe melasma versus an inactive control cream associated with IPL at 2 and 6 weeks. The melasma area severity index (MASI) was significantly lower with TC cream and IPL than with inactive cream and IPL at weeks 6 (P<0.0007) and 10 (P=0.002), and the treatment was well tolerated, although cutaneous irritation was greater with IPL plus TC cream than with IPL plus inactive cream (P<0.25 for all assessments).

In the authors’ opinion, IPL can be considered a valid therapeutic option—particularly in non-responders to conventional topical agents—however, only temporary and transient results can be achieved as there is repeat onset of hyperpigmentation lesions after a few weeks or months.

Fractional resurfacing is a novel concept of skin rejuvenation that has the potential to treat a variety of epidermal and dermal conditions. It produces a unique thermal damage pattern. In contrast to ablative skin resurfacing and non-ablative skin resurfacing, which achieve homogenous thermal damage at a particular depth, fractional resurfacing creates microscopic thermal lesions (i.e. MTZs). Fractional resurfacing specifically spares the tissue surrounding each MTZ, thus allowing for rapid re-epithelialisation and fast epidermal repair owing to the small size of the lesions and short migratory paths for the keratinocytes. In studies by Kroon et al, non-ablative 1550nm fractional laser therapy proved to be a safe treatment option for patients with darker skin types when topical bleaching was ineffective or not tolerated.

Niwa Massaki et al investigated the efficacy and safety of a single administration of a high-density fractional thulium fiber laser (1927nm) at 10 or 20mJ/cm² for the treatment of refractory melasma in 20 patients. Mean MASI scores decreased dramatically from 132.5±54 before treatment to 85.0±35 at 4 weeks after laser treatment (P=0.004). Patient assessment revealed that 12 of the 20 subjects had more than 50% clearance of their melasma. Recurrence was reported in seven out of 15 patients who were successfully followed-up (mean 10.2 months).

The biological role of cutaneous blood vessels in the pathogenesis of melasma is an interesting topic and opens new therapeutic perspectives. Recently, the authors performed a prospective study for evaluating the effects of pulsed dye laser (PDL) therapy. After a multispectral study for evaluating haemoglobin and melanin components, the authors are using this vascular laser with a low fluence and have obtained some notable improvements. It would be tempting to think that the action of PDL on vascularisation might have played an important role in preventing relapse. By targeting vascularisation and at least some part of the elastosis in the melasma lesions, it might be possible to decrease the stimulation of melanocytes and thus reduce the incidence of relapse.

**Conclusions**

All the laser devices discussed in this article represent new horizons for the treatment of hyperpigmentation disorders, and particularly in darker-skinned patients (Fitzpatrick skin types IV-VI). The use of lasers and pulsed light in the treatment of benign superficial pigmented lesions has revolutionised the possibilities of therapeutic responses available for the dermatologist.

Physical treatment with lasers (especially IPL) is usually limited to those patients who fail to respond to primary topical and cosmetic treatment. However, in the authors’ experience—and particularly in the treatment of melasma—it is only possible to obtain transient results with the likely reappearance of hyperpigmented lesions. Physical methods using lasers sometimes yield rebound hyperpigmentation.

The importance of the role of vascularisation in the pigmentation process must be studied further. This field of research may provide new therapeutic options, such as vascular lasers or anti-angiogenic agents. It is essential to carry out a precise clinical, dermatoscopic and multispectral evaluation of the pigmentation in order to select the most appropriate treatment and ensure adequate post-treatment care (photoprotection) and follow-up, as well as the quality and maintenance of...
results.

Declaration of interest none

Figures 1-7 © Dr Paolo Bonan et al

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